Remarks

I. Applicants' Claimed Compositions and Methods

Applicants have developed compositions and methods for improved transport across membranes, for the enhanced delivery of therapeutic and diagnostic agents, across, for example, cell membranes, such as those of endosomal vesicles within cells. The compositions include (1) a pH-sensitive polymer which does not disrupt cell membranes at or above physiological pH but which disrupts the cell membranes at low pH, for example, the low pH range inside the endosomes, in combination with (2) a second component which can be a carrier, diagnostic or therapeutic agent. The second component is conjugated to, complexed with or incorporated with the first polymer. When the second unit is a therapeutic or diagnostic agent, the composition can be provided in a carrier such as nanoparticles, microparticles, and liposomes.

Support for the amendments to claim 1 are found at page 6, line 5 and lines 15-18. These amendments clarify the claimed subject matter as a composition having two components:

(1) a membrane disruptive agent, and

(2) a carrier, therapeutic agent, or diagnostic agent, linked physically or chemically to the membrane disruptive agent.

Support for new claim 34 is found in example 1.

II. Rejections Under 35 U.S.C. § 112

Claims 1, 5, 7-13, 15, and 17-32 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The rejection is respectfully traversed if applied to the claims as amended.

Claim 1 has been rewritten in an attempt to clarify the claim language, and to provide

antecedent basis for claims 7, 11 and 26. It is well known that monomers, polymers or other chemical units can be coupled or linked to polymers via pendent side chains, or end termini. The scope of the claim has been amended so that the second unitis a carrier, a therapeutic or a diagnostic agent, or combination thereof.

Claim 9 refers to compounds which decrease lysosomal degradation. The examiner's attention is drawn to page 27, lines 8-16, which discusses the function of these compounds, as well as provides several representative compounds.

With respect to claim 22, "solvent composition" is described in the application at page 17, lines 5-17, however, there it is referred to under the general term of "other environmental stimuli". This specifically refers to changes in ion concentration, ion affinity and differential solubility, all of which can be altered by changing solvent composition.

III. Rejections Under 35 U.S.C. § 102

Claims 1, 5, 7, 9, 15, 18, 19, 21, 22, 28, and 29 were rejected under 35 U.S.C. § 102(a) as anticipated by U.S. Patent No. 5,609,590 to Herbig et al. ("Herbig"). Claims 1, 5, 7-13, 15, and 18-32 were rejected under 35 U.S.C. § 102(a) as anticipated by PCT WO 97/09068 by the Unversity of Washington ("University of Washington"). Claims 1, 5, 7, 9, 10, 15, 18-25 and 32 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,807,306 to Shapland et al. ("Shapland"). Claims 1, 3, 5, 8-13, 15, 17-19, 21, 22, 27 and 30 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,753,263 to Lishko et al. ("Lishko"). The rejections are respectfully traversed if applied to the amended claims.

As discussed above, the claims are drawn to a polymeric composition for enhancing

transport through lipid-containing membranes comprising

a first pH-sensitive polymer which is not hydrophobic at a first pH (typically at about pH 7.4), but which is hydrophobic and disrupts a lipid-containing membrane at a second pH (typically at between about 5 and about 6.5),

a second unit conjugated to, complexed with, or incorporated with the first pH- sensitive polymer, wherein the unit is a carrier, therapeutic or diagnostic agent.

A rejection under 35 U.S.C. §102 is only appropriate if the reference discloses each claimed element. The prior art discussed below fails to disclose each claimed element.

Herbig

Herbig in particular does not disclose a first pH-sensitive polymer which is not hydrophobic at a first pH, but which is hydrophobic and disrupts a lipid-containing membrane at a second pH, which is conjugated to, complexed with, or incorporated with a carrier, therapeutic agent or diagnostic agent.

Herbig discloses an osmotic drug delivery device that utilizes a pH sensitive material, that is semipermeable to water and causes hydrostatic pressure within the capsule to build and eventually burst the capsule, or is used to hold together two capsule portions until it degrades in contact with an environment having a particular pH such as in the stomach to release the capsule contents (col. 6, lines 40-58). The examiner is completely correct that this is a pH sensitive polymer, and could read on the situation where there is a blend of polymers. However, the purpose as well as the requisite components necessary to achieve that purpose are different. Herbig is designed to release drug in the gastrointestinal tract. The claims in this application are

drawn to a composition effecting release *intracellularly*. There is no mention of the second component of that blend (nor of any component of the device) *enhancing passage through a membrane* such as a cell wall or the endosomal membranes. The device is a bead or cylinder. The device is not a soluble or colloidal drug formulation. It is not foreseeable how a bead or cylinder could be effective in enhancing passage through a lipid membrane. There is simply nothing anywhere in the patent about a material that enhances passage through a lipid membrane. Therefore Herbig does not disclose the claimed invention.

University of Washington

This PCT application does disclose conjugates of pH and other stimuli-responsive polymers in combination with a variety of different molecules, including molecules that bind to ligands, nucleic acid molecules, but none that appear to enhance passage through a membrane, or enhance disruption of endosomal membranes, as defined by the claims. These other embodiments are now more clearly excluded by the amendments to claim 1. Figure 8 shows these constructs within the endosomes, where drug is released into the cytoplasm. The implication is that the drug is small and will "leak out" by simple passive diffusion across the endosomal membrane, without the membrane being disrupted. Figure 8 does ***not*** show the polymer ***disrupting the endosome*** so that drug is released from the endosome to the cytosol, as claimed. Figure 8 does not show the polymer ***as the means for effecting drug release to the cytosol.***

Since the University of Washington application does not disclose a two component system, one a stimulus-responsive polymer enhancing penetration of or passage through lipid

membranes, and the other a carrier, therapeutic or diagnostic agent, this application does not disclose the claimed invention.

Shapland

Shapland discloses a drug delivery apparatus and method for delivering a drug encapsulated in a polymeric matrix to internal body tissue using a catheter device and iontophoresis or phonophoresis (abstract). Shapland fails, however, to disclose or suggest a pH-sensitive polymer which is membrane disruptive at a pH between about 5 and 6.5 and which is conjugated to or has incorporated therein a carrier, therapeutic or diagnostic agent. Shaplund provides no teaching of altering membrane permeability, only of altering the rate of release of drug from a polymeric matrix in the catheter. Therefore Shapland does not disclose the claimed subject matter, or use thereof.

Lishko

Lishko discloses encapsulation of compounds in liposomes for targeted delivery to hair follicles (col. 3, lines 19-38). Additives include cryopreservatives and detergents (col. 15, line 57 to col. 16, line 36). It is undisputed that these liposomes could be useful for delivery of drugs including nucleic acids. Lishko fails, however, to disclose or suggest a pH-sensitive polymer which is membrane disruptive at a pH between about 5 and 6.5 and which is conjugated to or has incorporated therein a carrier, diagnostic or therapeutic agent. There is no mention of any compound enhancing disruption or penetration of a lipid containing membrane.

IV. Rejections Under 35 U.S.C. § 103

Claims 1, 3, 5, 8-13, 15, 17-19, 21, 22, and 27-31 were rejected under 35 U.S.C. § 103 as

obvious over Lishko. This rejection is respectfully traversed.

As discussed above, Lishko fails to disclose all of the claimed elements, in particular, a composition including a unit which enhances penetration of a lipid containing membrane, such as a cell wall or the membrane around an endosome. Lishko actually teaches away from the claimed subject matter, since Lishko teaches administering drug to hair follicles, which do not require penetration of a lipid containing membrane. In fact, a major reason why the hair follicle is selected as the site for delivery is not just to have an impact on the hair, but because delivery to the follicles is easier than delivery through the skin, which does require enhancing transport through cell membranes, or the tight junctions between cells.

Accordingly, Lishko not only does not disclose the claimed subject matter, nor make it obvious, but actually teaches away from it.

Applicants therefore respectfully request allowance of claims 1, 5, 7-13, 15, and 17-32, as amended.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Date: February 19, 2001
ARNALL GOLDEN & GREGORY, LLP
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450
(404) 873-8594
(404) 873-8595 (fax)

obvious over Lishko. This rejection is respectfully traversed.

As discussed above, Lishko fails to disclose all of the claimed elements, in particular, a composition including a unit which enhances penetration of a lipid containing membrane, such as a cell wall or the membrane around an endosome. Lishko actually teaches away from the claimed subject matter, since Lishko teaches administering drug to hair follicles, which do not require penetration of a lipid containing membrane. In fact, a major reason why the hair follicle is selected as the site for delivery is not just to have an impact on the hair, but because delivery to the follicles is easier than delivery through the skin, which does require enhancing transport through cell membranes, or the tight junctions between cells.

Accordingly, Lishko not only does not disclose the claimed subject matter, nor make it obvious, but actually teaches away from it.

Applicants therefore respectfully request allowance of claims 1, 5, 7-13, 15, and 17-32, as amended.

Respectfully submitted,

_____

Patrea L. Pabst
Reg. No. 31,284

Date: January 22, 2001
ARNALL GOLDEN & GREGORY, LLP
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450
(404) 873-8596
(404) 873-8597 (fax)

Certificate of Mailing under 37 CFR § 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Jean Hicks

Date: February 20, 2001

APPENDIX: Clean copy of claims as amended

1. (Twice amended) A polymeric composition for enhancing transport through membranes comprising

a first pH-sensitive polymer which is not hydrophobic at a first pH, but which is hydrophobic and disrupts a membrane at a second pH,

a second unit conjugated to, complexed with, or incorporated with the first pH- sensitive polymer, wherein the unit is selected from the group consisting of a carrier, a therapeutic agent, a diagnostic agent and combinations thereof.

5. (twice amended) The composition of claim 1 comprising a therapeutic or diagnostic agent, further comprising a pharmaceutically acceptable carrier.

7. (twice amended) The composition of claim 1 wherein the second unit comprises a polymer and the first polymer and the second unit form a graft copolymer, block copolymer, random copolymer or blend.

8. (twice amended) The composition of claim 1 wherein the second unit is linked to a ligand binding to the surface of a cell.

9. The composition of claim 1 further comprising a compound which decreases lysosomal degradation.

10. The composition of claim 5 wherein the therapeutic agent is a cytotoxic compound.

11. (twice amended) The composition of claim 1 wherein the second unit comprises a polycationic polymer.

12. (Once amended) The composition of claim 5 wherein the therapeutic agent is a

nucleoside, nucleotide, or nucleic acid.

13. (Once amended) The composition of claim 1 further comprising a carrier selected from the group consisting of microparticles, nanoparticles, micelles and liposomes.

15. (twice amended) A method for enhancing transport of agents through membranes comprising administering to the membrane any of the compositions of claims 1, 5, 7-13, and 26-32.

17. The method of claim 15 wherein the composition is administered to cells in a suspension.

18. The method of claim 15 wherein the composition is administered to layers of cells to enhance transport through the cell layers.

19. The method of claim 15 wherein the composition is administered to lipid membranes to enhance transport of molecules into or out of the lipid membranes.

20. (twice amended) The method of claim 15 wherein the composition is administered in combination with electrophoresis, ultrasound or iontophoresis.

21. The method of claim 15 further comprising application of a stimulus means to further enhance the effectiveness of the composition to disrupt the membrane, wherein the stimulus means induces a change in the structure of the polymer of the composition.

22. (twice amended) The method of claim 21 wherein the stimulus means is selected from the group consisting of changes in pH, light, ionic strength, solvent composition, temperature, and electric field.

23. The method of claim 15 further comprising administration of a stimulus means to

further enhance the effectiveness of the composition to disrupt the membrane, wherein the stimulus means is selected from the group consisting of ultrasound, electrical fields, radiation, and combinations thereof.

24. The method of claim 23 wherein the stimulus means is ultrasound.

25. The method of claim 24 wherein the ultrasound is administered at between 20 kHz and 10 MHz.

26. (amended) The composition of claim 11 wherein the polycationic material is selected from the group consisting of chitosan, polylysine, polyethyleneimine, poly(propyleneimine, aminodextran, collagen, polyvinylimidazole, and N,N-dimethylaminoethyl methylacrylate.

27. The composition of claim 13 wherein the carrier is a micelle or liposome.

28. (amended) The composition of claim 7 wherein the pH sensitive polymer is selected from the group consisting of acrylic acid; C_{1-6} straight chain, branched, ethylene-acrylic acid copolymers, and cyclic 2-alpha-alkyl acrylic acids; and esters of acrylic acid copolymerized with acrylic acid.

29. (amended) The composition of claim 7 wherein the second units comprise polymeric blocks comprising proteins or peptides which include imidazole groups.

30. (amended) The composition of claim 1 wherein the second unit comprises a lipid or phospholipid.

31. (amended) The composition of claim 1 wherein the second unit comprises sulfonated groups.

32. (amended) The composition of claim 1 wherein the second unit is sensitive to a stimulus selected from the group consisting of temperature, light, electrical stimuli, radiation, pH and ion concentration.

33. The composition of claim 1 wherein the membrane is an endosomal membrane and the first pH is approximately 7.4 and the second pH is between approximately 5.5 and 6.5.

34. The composition of claim 1 wherein the membrane is a cell membrane and the second pH is greater than 7.4.